Clinical Outcome of Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract. *BackgroundAim: We evaluated the efficacy and toxicities of three induction chemotherapy regimens in locally advanced head and neck cancer and assessed the clinical significance of human papillomavirus (HPV) in induction chemotherapy. Patients and Methods: Fifty-two patients were retrospectively evaluated; 12 patients received 5-fluorouracil-plus-cisplatin (FP); 24 patients received docetaxel-plus-cisplatin (DP); 16 patients received docetaxel, cisplatin, and 5-fluorouracil (TPF). Results: The TPF regimen showed a trend towards a higher overall response rate and pathological complete response and led to a significantly higher rate of metabolic complete response. Patients with HPV-positive tumors exhibited a significantly higher pathological complete response rate than those with HPV-negative tumors. In univariate analysis, the prognostic factors significantly affecting progression-free survival were lymph node stage, and metabolic and pathological complete response. Conclusion: TPF induction chemotherapy tended to improve clinical outcome, with manageable toxicity. Pathological complete response was positively correlated with HPV positivity.*

Multi-modal therapy consisting of surgery, radiation, and chemotherapy is most important for the management of locally advanced head and neck squamous cell carcinoma (HNSCC). However, the optimal sequence or prioritization of these various treatment methods remains controversial. The Meta-Analysis of Chemotherapy on Head and Neck Cancer Collaborative Group showed that concurrent chemoradiotherapy (CRT) had a 5-year absolute survival benefit of 6.5%, whereas there was no clear evidence of a benefit for induction chemotherapy (1, 2). Recently, phase III trials failed to demonstrate significant survival advantage with the addition of induction chemotherapy to CRT compared to CRT-alone (3, 4). According to these results, CRT is still widely accepted as the standard-of-care in the non-surgical management of patients with locally advanced HNSCC. Nevertheless, regarding distant failure, induction chemotherapy has shown a more significant and pronounced clinical benefit than CRT. Induction chemotherapy has also been associated with high tumor response rates correlated with favorable outcome; therefore, it could be a valuable treatment option. At this time, determination of predictive markers for long-term survival in patients receiving induction chemotherapy remains an important challenge.

During recent years changes have been witnessed in the regimen of induction chemotherapy for HNSCC. The most commonly used agents include platinum, 5-fluorouracil (5-FU), and taxanes. Since its development in the 1980s, the cisplatin-and-5-FU combination regimen (FP) has been the most extensively investigated regimen in the treatment of locally advanced HNSCC, with consistently high response rates (5). The taxane docetaxel has potent antitumor activity against recurrent and metastatic HNSCC, with an overall response rate between 21 and 42%, and the combination of docetaxel and cisplatin (DP) results in response rates from 40 to 71% (6). Recently, phase III trials have been conducted to compare induction chemotherapy using the FP doublet *versus* a three-drug combination of taxane, cisplatin and 5-FU (TPF) regimen. These studies have shown that TPF is superior to induction FP regarding progression-free survival (PFS) and overall survival (7, 8). Although these studies have reported that toxicity with TPF was no greater than that with FP, serious toxicities occurring with use of TPF are of the utmost concern in clinical practice.

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The discovery of the human papillomavirus (HPV) was an important advancement in the HNSCC field in the past decade. HPV status is an important molecular biomarker in the response to chemotherapy and CRT in patients with HNSCC. Consistent results from clinical trials of induction chemotherapy have been reported: patients with HPV-positive tumors have higher response rates after induction chemotherapy than patients with HPV-negative tumors (9).

The aims of the present study were to compare the antitumor efficacy and toxicities of induction chemotherapy regimens, including FP, DP, and TPF, for locally advanced HNSCC, and to investigate the clinical significance of HPV in induction chemotherapy.

Patients and Methods

Patients. Sixty-one patients with locally advanced unresectable head and neck cancer received induction chemotherapy at the Seoul St. Mary's Hospital between January 2002 and December 2012. We excluded five patients with nasopharyngeal carcinoma and salivary gland tumors, and four patients with histological subtype other than squamous cell carcinoma. Ultimately, 52 patients were included in the study, and clinical records and pathology reports were reviewed retrospectively. The following clinical data were collected: age, sex, smoking history, comorbidity, tumor site, staging, surgery, chemotherapy, radiotherapy, recurrence, and survival. Ethical Committee approval was obtained from the Institutional Review Board of The Catholic University of Korea, Seoul St. Mary's Hospital (No. KC13SISI0693), and an informed consent was provided.

Induction chemotherapy and response evaluation. Induction chemotherapy was administered with the following three regimens in accordance with the physician's decision. The FP regimen consisted of an intravenous infusion of 100 mg/m^2 cisplatin on day 1, followed by a 24-h continuous infusion of 1,000 mg/m^2 5-FU for five days. The DP regimen consisted of an intravenous infusion of 70 mg/m^2 docetaxel and 70 mg/m^2 cisplatin on day 1. The TPF regimen consisted of an intravenous infusion of 70 mg/m^2 docetaxel and 70 mg/m^2 cisplatin on day 1, followed by a 24-h continuous infusion of 700 mg/m^2 5-FU for four days.

After two or three cycles of induction chemotherapy, response evaluation was performed by computed tomographic (CT) scan, magnetic resonance imaging (MRI), or ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)-CT. Response evaluation was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) (10). Toxicity was assessed according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (version 4.0) (11), and the worst toxicity observed during chemotherapy was recorded. Metabolic tumor response was assessed according to the Standardized uptake value (SUV) measurement criteria of the European Organization for Research and Treatment of Cancer (12). Metabolic complete response (mCR) is defined as complete resolution of FDG uptake in the tumor such that activity is less intense than the liver and indistinguishable from surrounding background blood pool levels.

Treatment plans were determined by a head and neck cancer multidisciplinary team consisting of a medical oncologist, radiation oncologist, surgical oncologist, pathologist, radiologist, and nuclear

Table I. *Clinicopathological characteristics according to induction chemotherapy regimen*.

Characteristic	All patients (n=52)	FP (n=12)	Docetaxel-containing regimens		*p*-Value
			DP (n=24)	TPF (n=16)	
Age, years					0.153
Mean±SD	60.2±9.3	64.4±7.4	59.8±11.0	57.6±6.6	
Gender					0.382
Men	45 (86.5)	9 (75.0)	22 (91.7)	14 (87.5)	
Women	7 (13.5)	3 (25.0)	2 (8.3)	2 (12.5)	
Smoking					0.023
Current/ex-smoker	34 (65.4)	4 (33.3)	19 (79.2)	11 (68.8)	
Non-smoker	18 (34.6)	8 (66.7)	5 (20.8)	5 (31.2)	
Alcohol use					0.187
Yes	30 (57.7)	5 (41.7)	17 (70.8)	8 (50.0)	
No	22 (42.3)	7 (58.3)	7 (29.2)	8 (50.0)	
ECOG					0.080
0	12 (23.1)	0	8 (33.3)	4 (25.0)	
1	40 (76.9)	12 (100)	16 (66.7)	12 (75.0)	
No. of comorbidities					0.318
0-1	39 (75.0)	8 (66.7)	17 (70.8)	14 (87.5)	
2-4	13 (25.0)	4 (33.3)	7 (29.2)	2 (12.5)	
Primary cancer site					0.619
Oropharynx	39 (75.0)	8 (66.6)	17(70.8)	14 (87.5)	
Hypopharynx	7 (13.5)	2 (16.7)	3 (12.5)	2 (12.5)	
Larynx	6 (11.5)	2 (16.7)	4 (16.7)	0	
cT stage					0.931
T1-2	32 (61.5)	7 (58.3)	14 (58.3)	11 (68.7)	
T3-4	20 (38.5)	5 (41.7)	10 (41.7)	5 (31.3)	
cN stage					0.553
N0-1	8 (15.4)	4 (33.3)	3 (12.5)	1 (6.3)	
N2-3	44 (84.6)	8 (66.7)	21 (87.5)	15 (93.7)	
Grade (n=47)					0.321
Well	2 (4.3)	0	0	2 (13.3)	
Moderate	30 (63.8)	6 (66.7)	16 (69.6)	8 (53.4)	
Poorly	15 (31.9)	3 (33.3)	7 (30.4)	5 (33.3)	
Further treatment after ICT					0.843
Surgery alone	5 (9.6)	0	3 (12.5)	2 (12.5)	
Surgery followed by RT	23 (44.2)	6 (50.0)	9 (37.5)	8 (50.0)	
Definitive CRT	21 (40.4)	5 (41.7)	11 (45.8)	5 (31.2)	
No treatment	3 (5.8)	1 (8.3)	1 (4.2)	1 (6.3)	
HPV status (n=42)					0.403
Positive	16 (38.1)	2 (22.2)	7 (36.8)	7 (50.0)	
Negative	26 (61.9)	7 (77.8)	12 (63.2)	7 (50.0)	
p16 status (n=41)					0.509
Positive	24 (58.5)	4 (44.4)	11 (57.9)	9 (69.2)	
Negative	17 (41.5)	5 (55.6)	8 (42.1)	4 (30.8)	
p53 status (n=43)					0.806
Positive	28 (65.1)	7 (70.0)	12 (60.0)	9 (69.2)	
Negative	15 (34.9)	3 (30.0)	8 (40.0)	4 (30.8)	

ECOG, Eastern Cooperation Oncology Group; ICT, induction chemotherapy; RT, radiotherapy; CRT, concurrent chemoradiotherapy; HPV, human papillomavirus; FP, 5-fluorouracil + cisplatin; DP, taxane + cisplatin; TPF, docetaxel + cisplatin + 5-fluorouracil.

Table II. *Response rates according to induction chemotherapy regimen.*

Response	FP (n=12)	DP (n=24)	TPF (n=16)	*p*-Value
Clinical response				
CR	2 (16.7)	3 (12.5)	4 (25.0)	0.680
PR	9 (75.0)	16 (66.7)	11 (68.7)	
SD	0	3 (12.5)	1 (6.3)	
PD	1 (8.3)	2 (8.3)	0	
Overall response	11 (91.7)	19 (79.2)	16 (97.8)	0.349
Metabolic response				
CR	1 (25.0)	2 (11.8)	9 (75.0)	0.002
Non-CR	3 (75.0)	15 (88.2)	3 (25.0)	
Pathological response				
CR	2 (33.3)	4 (33.3)	5 (50.0)	0.688
Non-CR	4 (66.7)	8 (66.7)	5 (50.0)	

FP, 5-Fluorouracil + cisplatin; DP, taxane + cisplatin; TPF, docetaxel + cisplatin + 5-fluorouracil; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

Table III. *Response rates according to HPV status.*

Response	HPV-positive (n=16)	HPV-negative (n=26)	*p*-Value
Clinical response			
CR	4(25.0)	2 (7.7)	0.264
PR	11 (68.7)	19 (73.1)	
SD	0	3 (11.5)	
PD	1 (6.3)	2 (7.7)	
Overall response	15 (93.8)	21 (80.7)	0.243
Pathological response (n=25)			
CR	6 (66.7)	4 (25.0)	0.041
Non-CR	3 (33.3)	12 (75.0)	

CR, Complete response; PR, partial response; PD, progressive disease; SD, stable disease; HPV, human papillomavirus.

Table IV. *Univariate survival analysis according to clinicopathological variables.*

Variable		All patients (n=52)	
		1-Year PFS (%)	*p*-Value
Primary site	Oropharynx	76.3	0.817
	Hypopharynx	71.4	
	Larynx	50.0	
Smoking history	Current/ex-smoker	66.7	0.365
	Non-smoker	83.3	
T Stage	1-2	80.6	0.093
	3-4	60.0	
N Stage	0-1	100.0	0.038
	2-3	68.2	
Induction chemotherapy	Doublet	63.9	0.085
	Triplet	93.7	
Histological grade	Well/moderate	71.9	0.879
	Poor	73.3	
HPV status	Positive	82.3	0.303
	Negative	65.4	
p16	Positive	76.0	0.589
	Negative	64.7	
p53	Positive	75.0	0.221
	Negative	60.0	
Pathological CR after ICT	Yes	100.0	0.015
	No	61.1	
Metabolic CR after ICT	Yes	100.0	0.037
	No	61.9	

HPV, Human papillomavirus; CR, complete response; ICT, induction chemotherapy.

medicine physician. Based on the assessment of response and patients' preference, either curative surgical resection followed by adjuvant radiotherapy (RT)/CRT or definitive CRT was conducted after induction chemotherapy. CRT was performed using a standard radiotherapy technique of once daily 2.1 Gy per fraction for five days, for a total dose 65-70 Gy. Concomitantly administered chemotherapy regimens included weekly cisplatin (30 mg/m^2, day 1) or tri-weekly cisplatin (100 mg/m^2, day 1) or weekly 5-FU (1,000 mg/m^2, day 1) and cisplatin (30 mg/m^2, day 1).

Pathology. The presence of HPV was assessed by in situ hybridization. *In situ* hybridization was processed on the automated Benchmark system from Ventana Medical Systems using the INFORM® HPV III Family 16 Probe (cocktail of HPV subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 66; Ventana Medical Systems lnc., Tucson, AZ, USA) as per manufacturer's recommendations. When HPV is integrated, the HPV hybridization signal is seen as punctuate nuclear staining. Immunohistochemistry assays for p16^{INK4A} (mouse monoclonal antibody to p16, 1:200; Santa Cruz Biotechnology lnc., Santa Cruz, CA, USA) and p53 (DO-7, 1:200; Ventana Medical Systems Inc., Tucson, AZ, USA) were performed using the Ventana NX automated immunohistochemistry system (Ventana Medical Systems). Expression of p16 was scored as positive if strong and diffuse nuclear and cytoplasmic staining was present in 70% or more of the tumor specimen. Expression of p53 was scored as positive if strong nuclear staining was present in 10% or more of the tumor specimen. Pathological complete response (pCR) is defined as the absence of residual tumor cells in either primary tumor sites or cervical lymph nodes. The results were interpreted by an independent pathologist who was blinded to the prognosis of each case.

Statistical analysis. Student's *t*-test and analysis of variance (ANOVA) were used to evaluate significant differences among the continuous variables. Categorical variables were compared using the chi-square test and Fisher's exact test. To determine the significance and strength of bivariate associations, we used Spearman's rank correlation coefficient. PFS was defined as the time from the date of first chemotherapy to the date of first observation of disease progression, relapse, or death due to any cause. Univariate analysis and survival curves were estimated using the Kaplan–Meier method and the log-rank test was applied to identify differences. A *p*-value of less than 0.05 was considered statistically significant.

Table V. *Toxicity profiles according to the induction chemotherapy regimen.*

Toxicity	FP (n=12)		DP (n=24)		TPF (n=16)	
	Grade, n (%)		Grade, n (%)		Grade, n (%)	
	1/2	3/4	1/2	3/4	1/2	3/4
Neutropenia	3 (25.0)	3 (25.0)	0	22 (91.7)	4 (25.0)	10 (62.5)
Febrile neutropenia	0	2 (16.7)	0	3 (12.5)	0	2 (12.5)
Raised Cr level	0	0	0	0	1 (6.3)	0
Asthenia	5 (41.7)	1 (8.3)	13 (54.2)	5 (20.8)	9 (56.3)	0
Myalgia	0	0	4 (16.7)	0	1 (6.3)	0
Anorexia	2 (16.7)	1 (8.3)	8 (33.3)	2 (8.3)	6 (37.5)	1 (6.3)
Nausea	5 (41.7)	0	15 (62.5)	1 (4.2)	5 (31.3)	0
Mucositis	5 (41.7)	2 (16.7)	12 (50.0)	2 (8.3)	6 (37.5)	1 (6.3)
Diarrhea	2 (16.7)	0	6 (25.0)	1 (4.2)	9 (56.2)	2 (12.5)
Neuropathy	2 (16.7)	1 (8.3)	6 (25.0)	0	1 (6.3)	0

FP, 5-Fluorouracil + cisplatin; DP, taxane + cisplatin; TPF, docetaxel + cisplatin + 5-fluorouracil; Cr, creatinine.

Results

Patients' characteristics. The clinicopathological characteristics of the 52 patients are summarized in Table I. The mean age of the patients was 60.2 (range=29-75) years. The primary tumor site in the majority of cases was the oropharynx (75.0%). Among the 52 patients, FP was given to 12 (23.0%) patients, DP to 24 (46.2%) patients, and TPF to 16 (30.8%) patients. There were no significant differences in baseline characteristics between FP, DP, and TPF groups except for smoking history (Table I). After induction chemotherapy, 28 (53.8%) patients underwent surgery with curative intent; five underwent surgery alone, and 23 underwent surgery followed by adjuvant RT or CRT. Twenty-one patients underwent induction chemotherapy followed by definitive CRT without surgical resection. Two patients did not receive further treatment due to chemotherapy-related toxicity, and one patient did not receive further treatment after achieving a clinical CR after induction chemotherapy.

Clinical outcome of induction chemotherapy. The overall response rate (ORR) for all patients who received induction chemotherapy was 86.5%, with 17.3% achieving clinical CR, and three patients underwent disease progression even after induction chemotherapy. Among the 28 patients who underwent surgery after induction chemotherapy, 11 (39.3%) had a pCR. Twelve (36.3%) out of the 33 patients examined by PET-CT before and after induction chemotherapy achieved mCR. A comparison of the response outcomes between the three induction chemotherapy regimens is summarized in Table II. The TPF regimen showed a trend towards achieving a higher CR and pCR rate than the doublet regimens, but the differences were not statistical significant. In the assessment of the metabolic response by PET-CT scan, the TPF regimen also had a significantly higher rate of mCR (p=0.002). We assessed response outcomes according to HPV, p16, and p53 status. There was no significant differences in ORR according to HPV status, but patients with HPV-positive HNSCC had a significantly higher rate of pCR (p=0.041) (Table III). In the assessment of mCR, patients with HPV-positive HNSCC showed a trend towards a higher rate of mCR, but the differences were not statistically significant. Response rates did not differ according to p16 or p53 positivity. The expression of p16 was positively correlated with tumor HPV status (r=0.647; p=0.001) (data not shown).

Recurrence and survival analysis. The median follow-up was 24.1 months. Thirty-seven (71.2%) out of the 52 patients achieved clinical CR after completion of the planned treatments including surgery or CRT. Among these 37 patients, recurrence occurred in eight, with five experiencing locoregional recurrences and three with distant metastases. In patients with pCR after induction chemotherapy there were no recurrences, whereas about half of the patients with non-pCR experienced recurrence. Three patients underwent disease progression even after induction chemotherapy and five patients underwent progression after induction chemotherapy followed by CRT.

Only two (12.5%) out of the 16 patients who received TPF had recurrence or progression, whereas 11 (41.8%) out of the 24 patients receiving DP and five (41.6%) out of the 12 patients receiving FP experienced recurrence or progression (p=0.080). Seven (26.9%) out of the 26 patients with either HPV-positive or p16-positive tumors experienced recurrence or progression, whereas eight (47.0%) out of the 17 patients with both HPV-negative and p16-negative tumor experienced recurrence or progression (p=0.176). In univariate analysis, the prognostic

factors significantly affecting PFS were N stage, mCR, and pCR after induction chemotherapy (Table IV).

Dose intensity and toxicity of induction chemotherapy. The median number of cycles of induction chemotherapy was three (range=1-6). Thirty-one (59.6%) out of the 52 patients received full-dose chemotherapy, 13 (25.0%) received reduced dose chemotherapy from the first cycle, and eight (15.4%) patients received a dose reduction during chemotherapy. The relative dose intensity (delivered dose:planned dose) was 85% for DP and 84% for FP; that for TPF was 91% for docetaxel, 86% for cisplatin, and 94% for 5-FU.

The toxicity profiles are listed in Table V. The taxane-containing regimen led to more frequent neutropenia, but there were no significant differences in hematological and non-hematological toxicities between the FP, DP, and TPF regimens.

Discussion

Induction chemotherapy followed by definitive CRT or surgery is used as an option for the treatment of patients with locally advanced HNSCC in daily practice. Despite high response rates and reduction of distant metastases, induction chemotherapy has failed to show a significant survival benefit compared with locoregional treatment. These results have led to an effort to seek newer induction chemotherapy regimens to improve clinical outcome. In the TAX-324 and TAX-323 trials, TPF had a statistically significant benefit in PFS and overall survival over FP (7, 8). Blanchard *et al*. used meta-analysis to show that the induction of TPF is superior to induction of FP for overall survival, PFS, locoregional failure and distant failure (12). On the basis of these results, TPF should be considered the most effective induction chemotherapy regimen; however, concerns about the toxicity of the triple-drug regimen have limited practical use in oncological clinics.

In our study, the TPF regimen was modified, with a lower dose than that used in TPF during the TAX-323 and -324 trials because of concerns about toxicity. Despite the lower doses, the TPF regimen tended towards higher ORR, pCR, and mCR and a lower incidence of relapse or progression compared with the DP and FP regimens. There was no significant difference in toxicity between the three regimens. The most common criticism about induction chemotherapy is that it may interfere with planned locoregional treatment due to chemotherapy-induced toxicity. We confirmed that only two patients did not receive the planned treatment after induction chemotherapy because of pneumonia and general weakness occurring immediately after chemotherapy. One patient received DP, and the other received FP. We found that the relative dose intensity of TPF was higher than that of FP and DP, and the incidence of major toxicity with the TPF regimen was relatively lower than that of previous studies. This could be due to the relatively low dose, young age of the TPF group and aggressive supportive care. These factors are thought to have contributed to the improved patient compliance and clinical outcome of the TPF regimen. Therefore, with cautious selection of candidate patients and aggressive supportive care, TPF is thought to be a relatively tolerable induction chemotherapy regimen for locally advanced HNSCC, with a good clinical outcome.

In recent years, HPV has emerged as one of the important prognostic factors in HNSCC. HPV-positive HNSCC is a distinct disease entity with unique clinical features. Previous studies have reported that patients with HPV-positive tumors have a more favorable survival and treatment response to chemotherapy and radiotherapy than patients with HPV-negative tumors (13-15). Posner *et al*. reported in the follow-up study of TAX-324 that patients with HPV-positive oropharyngeal cancer had better PFS and overall survival than those with HPV-negative oropharyngeal cancer, regardless of whether the TPF or FP induction chemotherapy regimen was administered (14). We found that those with HPV-positive tumors had a significantly higher pCR rate compared with those with HPV-negative tumors. Patients with HPV-positive tumors tended to have a longer PFS than patients with HPV-negative tumors, but there was no statistically significant difference. The relatively high smoking rate in our patients may have affected these results. Smoking is a well-known factor of poor prognosis in HNSCC and it may reduce the favorable outcome linked to HPV-related pathogenesis.

Two randomized phase III trials, DeCIDE and PARADIGM, were planned to evaluate the role of induction chemotherapy by comparing induction chemotherapy followed by CRT with CRT alone; negative results from both studies were recently presented (3, 4). However, the two clinical trials had some limitations. Firstly, these two studies terminated early due to slow accrual and so did not fulfill the planned sample size. The reduced sample size of the study may also have had a negative influence on the results. Additionally, the two studies were designed prior to the emergence of HPV as an important prognostic factor and patients in these trials were not stratified according to HPV status. Thus, the role of induction chemotherapy according to HPV status is not yet clear and these issues should be investigated by additional subset analysis.

In our study, none of the patients achieving pCR after induction chemotherapy experienced recurrence or progression regardless of the type of chemotherapy regimen and their HPV status. The statistical analysis of PFS indicated that pCR after induction chemotherapy was a significant prognostic factor for PFS in HNSCC. Previous studies have shown that pCR after neoadjuvant chemotherapy is associated with better clinical outcome and survival in various types of cancer such as breast cancer and colorectal cancer (16-18). Recently, Zhang *et al*.

reported that pCR achieved by neoadjuvant chemotherapy could lead to improved locoregional control and long-term survival in patients with advanced HNSCC (19). These results strongly support the expectation that patients with locally advanced HNSCC achieving pCR after induction chemotherapy could have long-term survival. Therefore, translational research for the predictive markers for tumor response in patients receiving induction chemotherapy for HNSCC is needed. Further studies are also needed for better selection and identification of patients who can benefit from induction chemotherapy. We assessed the role of p16 and p53 with HPV status as predictive markers for tumor response of induction chemotherapy, but did not find any significant associations.

In conclusion, there was a trend towards improved clinical outcome with TPF induction chemotherapy in patients with locally advanced HNSCC, and the toxicities were mostly manageable. Patient selection and more specialized, aggressive supportive care are most important in improving the treatment outcome of induction chemotherapy. Patients with HPV-positive tumors had a significantly higher rate of pCR than patients with HPV-negative tumors. Achieving a pCR after induction chemotherapy for HNSCC is a strong predictive indicator of PFS, and further research on the predictive factors of pCR is required.

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